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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,704	06/01/2007	Maria Isabel Crespo Crespo	LABO-003/02US 311815-2022	6572

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EXAMINER	
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ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,704	CRESPO CRESPO ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,14,16,18,19 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,16,18,19 and 28* is/are rejected.

7)☒ Claim(s) *5,6 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070731*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8, 14, 16, 18-19 and 28 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 18 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating asthma; and a pharmaceutical composition comprising the a compound of formula (I), does not reasonably provide enablement for a method of treating all other diseases listed in claims 16 and 18, namely: ischemia, supravetricular arrhythmias, acute renal failure, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, myocardial reperfusion injury, diabetes mellitus, obesity, inflammatory bowel diseases, Parkinson's disease, Huntington's disease, dystonias, restless leg syndrome or dyskinesias; or a pharmaceutical composition comprising a compound of formula (I) and another compound listed in claim 28. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working

examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 28 is drawn to 'a pharmaceutical composition comprising a compound of formula (I) and another compounds selected from dopamine antagonists, inhibitor of dopamine decarboxylase, …'. First, the specification does not provide sufficient written description regarding such combination compositions. The specification at page 8 generically lists the drugs intended for the combination, however, does not provide any specific examples of the compounds having the activity. The scope of the instant claim includes agents that are known and those that may be discovered in future, for which there is no enablement. Specifically, the specification include generic groups or agents such as dopamine antagonists, inhibitor of dopamine decarboxylase, etc. all of which may include numerous species and there is insufficient guidance in the specification to enable one of ordinary skill in the art how the compounds of the invention and the other biological agent provide a synergistic activity to achieve the desired results.

The specification fails to enable one skilled in the art to use the instantly claimed compounds. The use disclosed in the specification is that the compounds selectively bind to adenosine A_{2A} receptors and are therefore, useful to treat a variety of diseases, see specification pages 43-44. Biological assays to test the binding activity of the compounds is provided at page 43, and the IC_{50} ranges for the A_{2a} receptor binding affinity of the instant compounds was provided. However, the specification does not provide how this activity links to the treatment of

all types of disorders of the instant claim and there is no reasonable basis for assuming that the myriad of compounds embraced by the instant claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art (directed to adenosine A_{2a} receptors) for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also, see MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally an unpredictable and highly structure specific area.

The specification provides that the diseases associated with adenosine A_{2b} receptors include diverse list of diseases, many with different etiologies such as asthma, ischemia, supravetricular arrhythmias, acute renal failure, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, myocardial reperfusion injury, diabetes mellitus, obesity, inflammatory bowel diseases, Parkinson's disease, Huntington's disease, dystonias, restless leg syndrome or dyskinesias. It is inconceivable as to how the claimed single class of compounds can treat the vast list of diseases recited in the claims having diverse mechanisms. See the unpredictability of the ligand-receptor interactions reported in state of the art. Baraldi et al. (Current Pharmaceutical Design, 2002) indicated that "except for some xanthine derivatives reported by Jacobson and coworkers, no potent and selective compounds as human A2b antagonists are reported" (see page 2318). While the xanthine derivative reported in the reference had a binding affinity of 1.97nM (see page 2310), applicant reported an affinity of <100nM for the instant compounds – which raises a question whether or not applicant's compounds are within the same range in binding affinity as the compounds of the reference. The

high affinity of Jacobson's compounds to the hA_{2B} compared to the vague description of the activity and related K_i values of instant compounds casts reasonable doubts whether the compounds truly have the adenosine A_{2b} receptor binding activity.

Further, the state of the art provides the activity of adenosine receptors in the treatment of asthma (see Feoktistov et al., page 394), however, the state of the art does not provide compounds having adenosine A_{2a} binding activity as therapeutic agents for all of the instantly recited conditions or disorders. In fact, Feoktistov, provides that "The biggest problem in translating this knowledge into therapeutic tools is perhaps the ubiquity of adenosine receptors, which often mediate contrasting effects. The challenge is how to develop drugs that will selectively target a receptor mediating a specific action. The ongoing development of selective agonists or antagonist represents a substantial advancement toward this goal. Nonetheless, even if specific agents can be developed for a given receptor subtype, the problem remains of selectively targeting the site of action" (see page 396). Therefore, the state of the art provides that the adenosine receptor activity is very unpredictable, which emphasizes the requirement of undue experimentation in determining the corresponding therapeutic activity.

There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'method for treating ischemia, supravetricular arrhythmias, acute renal failure, allergic reactions including but not limited to

rhinitis, urticaria, scleroderm arthritis, myocardial reperfusion injury, diabetes mellitus, obesity, inflammatory bowel diseases, Parkinson's disease, Huntington's disease, dystonias, restless leg syndrome or dyskinesias' solely based on the activity disclosed for the compounds.

Further, the use of the compounds according to the specification includes treatment of inflammatory bowel diseases such as ulcerative colitis, which have been proven very difficult to treat because 'there is no known cause' (see The Merck Manual <http://www.merck.com/mrkshared/mmanual/section3/chapter31/31c.jsp>). The therapeutic method of the instant claims includes treatment of inflammatory bowel disease, e.g., Crohn's disease, ulcerative colitis, etc. which have been proven very difficult to treat because 'there is no known cause' (see The Merck Manual). Singh et al. (British Journal of Surgery, 2001) provide that 'the etiology and pathogenesis of inflammatory bowel diseases are incompletely understood' (see page 1558). Robinson (Eur. J. Surg. 1998) indicates that "Despite the growing list of medications and formulations prompted for the treatment of IBD, no single drug or recognized combination has yet been confirmed as dependably clinically effective"; "All physicians who care for UC and CD patients enthusiastically await more optimal regimens for these challenging disorders" (see page 90). This state of the art analysis indicative of the unpredictability related to the treatment of inflammatory bowel diseases.

Further, the instant claims recite method of treating numerous diseases. First, the instant claims appear to be in 'reach through' format. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through to the corresponding therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue

experimentation for one of skill in the art to practice the invention. Further, there is no disclosure regarding how the patient in need of the specific enzymatic activity or suffering from a condition mediated by the recited mode of action, is identified and further, how the appropriate therapeutic effect is generally produced in the patient. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds in the instantly claimed method of treatment.

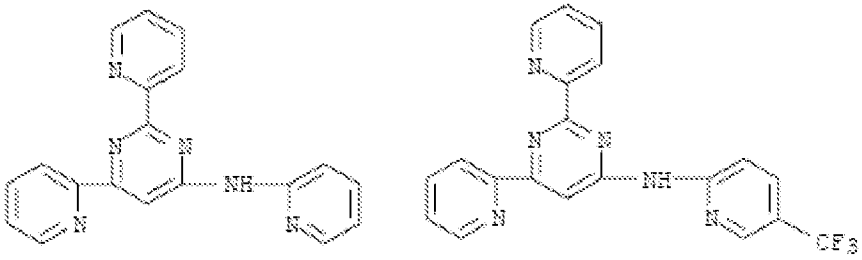
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7-8, 16, 18-19 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Wang et al., WO 2005/099711 (effective filing date April 13, 2004). The instant claims read on reference disclosed compounds, see the structural formula (I) in page 5 and the corresponding species of the Examples, specifically the last two compounds listed in the Table on page 52 (depicted below for convenience):

(2,6-Di-pyridin-2-yl-pyrimidin-4-yl)-pyridin-2-yl-amine
(2,6-Di-pyridin-2-yl-pyrimidin-4-yl)-(5-trifluoromethyl-pyridin-2-yl)-amine



The compounds are taught to be useful as pharmaceutical therapeutic agents for the treatment of Parkinson's disease, ischemia, etc. see page 32.

Note: Acknowledgment is made of applicant's claim for foreign priority based on an application P200302951, filed in Spain on December 15, 2003. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7-8, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cai et al., WO 02/47690. The reference teaches a generic group of 2,6-di-heteroaryl-4-(hetero)arylaminopyrimidine compounds, which embraces applicant's instantly claimed compounds. See formula (II) in page 11 and the corresponding species of the examples, particularly, Examples 109-114 (pages 92-94 and 140-141). The compounds are taught to be useful as pharmaceutical therapeutic agents, see pages 40-41.

Either or both of the following situations apply for the instant claims.

1. The instant claims differ from the reference by reciting specific species or a more limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the

reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents.

2. The instant claims exclude the reference disclosed compounds (see the proviso statement), however, include the structural analogs of the reference disclosed compounds. For example, the instant claims exclude the reference compound: 4-(3-methoxyanilino)-2,6-di(2-pyridinyl)pyrimidine, however, include compounds wherein, for example, the methoxy is on a different position of the phenyl (i.e., 2- or 4-position); or one of the pyridine rings is attached from its 3- or 4-position, etc. Alternatively, there is a methyl substituent on one of the rings in place of hydrogen. As can be seen there are number possibilities of structural analogs of the reference disclosed compounds and these are taught and/or suggested in the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents.

One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck*

& Co. v. Biocraft Laboratories, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989). *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950); *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

Allowable Subject Matter

Claims 5-6 and 14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The references of record do not teach or fairly suggest the compounds according to these claims.

Receipt is acknowledged of the Information Disclosure Statement filed on July 31, 2007 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

March 8, 2010